IN THE CLAIMS

Please cancel claims 61, 62, 68 and 72-74 and amend claims 1, 3, 4, 6-9, 11, 16, 18-26, 29, 31-39, 41-45, 48-54, 56-60, 63-65, 67, 69-71, 75, 76, 78-86, and 88-91 in accordance with the following listing showing the status of all claims in the application:

1. (Currently Amended) A method of probing for a nucleic acid comprising:

contacting a nucleic acid solution with an oligonucleotide probe ~~labelled~~labeled with an electrochemically active marker~~,~~;

providing conditions at which the probe is able to at least partially ~~hybridise~~hybridize with any complementary target sequence which may be present in the nucleic acid solution~~,~~;

selectively degrading either ~~hybridised~~hybridized, partially ~~hybridised or unhybridised~~hybridized or unhybridized nucleic acid probe~~,~~; and

electrochemically determining information relating to the electrochemically active marker.

2. (Original) A method as claimed in claim 1 wherein the information relating to the marker is used to derive information concerning the presence or absence of at least one nucleic acid species.

3. (Currently Amended) A method as claimed in claim 1 ~~or claim 2~~ wherein the electrochemical technique is used to quantify relative proportions of degraded and non-degraded probe.

4. (Currently Amended) A method as claimed in ~~any one of claims~~claim 1 ~~to 3~~ wherein nucleic acid probe that has failed to successfully ~~hybridise~~hybridize is digested by an enzyme that has been chosen to selectively digest single stranded ~~unhybridised~~unhybridized nucleic acid.

5. (Original) A method as claimed in claim 4 wherein the enzyme is an endonuclease.

6. (Currently Amended) A method as claimed in claim 4 ~~or claim 5~~ wherein the enzyme is a ribonuclease.

7. (Currently Amended) A method as claimed in claim 4 ~~or claim 5~~ wherein the enzyme is a deoxyribonuclease.

8. (Currently Amended) A method as claimed in ~~any one of claims 4 to 7~~claim 4 wherein the enzyme is S1 deoxyribonuclease.

9. (Currently Amended) A method as claimed in claim ~~4, claim 5 or claim 7~~4 wherein the enzyme is an exonulcease.

10. (Original) A method as claimed in claim 9, wherein the enzyme is T7 exonuclease.

11. (Currently Amended) A method as claimed in ~~any one of claims~~claim 1 ~~to 3~~ wherein nucleic acid probe that has successfully ~~hybridised~~hybridized is digested by an enzyme that has been chosen to selectively digest at least one strand of double stranded ~~hybridised~~hybridized nucleic acid.

12. (Original) A method as claimed in claim 11 wherein the enzyme is a 5' nuclease.

13. (Original) A method as claimed in claim 12 wherein the 5' nuclease is also a DNA polymerase.

14. (Original) A method as claimed in claim 13 wherein the 5' nuclease/ DNA polymerase is a thermostable enzyme.

15. (Original) A method as claimed in claim 14 wherein the thermostable enzyme is Taq polymerase.

16. (Currently Amended) A method as claimed in claim 14 ~~or claim 15~~ wherein the ~~reaction mixture~~nucleic acid solution also comprises a pair of primers suitable for extension by the DNA polymerase.

17. (Original) A method as claimed in claim 16 wherein reaction conditions and temperature cycling are suitable for a polymerase chain reaction (PCR) to take place concomitant to the 5' nuclease digestion of probe.

18. (Currently Amended) A method as claimed in ~~any one of claims 1 to 3,~~claim 1, in which a first oligonucleotide probe ~~labelled~~labeled with an electrochemically active marker is prevented from complete ~~hybridisation~~hybridization by competition from a second oligonucleotide, and the resultant partially ~~hybridised~~hybridized oligonucleotide ~~labelled~~labeled with an electrochemically active marker is cleaved by an enzyme that specifically ~~recognises~~recognizes the configuration of the two oligonucleotides ~~hybridised~~hybridized onto the target nucleic acid, said cleavage effectively shortening the oligonucleotide portion to which the electrochemically active marker is attached.

19. (Currently Amended) A method as claimed in ~~any one of claims 1 to 3,~~claim 1, in which a first oligonucleotide probe is prevented from complete ~~hybridisation~~hybridization by competition from a second oligonucleotide, and the resultant partially ~~hybridised~~hybridized first oligonucleotide probe is cleaved by an enzyme that specifically ~~recognises~~recognizes the configuration of the two oligonucleotides ~~hybridised~~hybridized onto the target nucleic acid, the cleavage product being ~~recognised~~recognized by a recognition cassette which comprises at lease one oligonucleotide and is able to ~~hybridise~~hybridize to the first cleavage product to produce an oligonucleotide configuration ~~recognisable~~recognizable by an enzyme that cleaves a region of the recognition cassette that is ~~labelled~~labeled with an electrochemically active marker.

20. (Currently Amended) A method as claimed in ~~any one of the preceding claims~~claim 1 wherein the electrochemically determined information is used for the detection of nucleic acid polymorphisms.

21. (Currently Amended) A method as claimed in ~~any one of the preceding claims~~claim 1 wherein the electrochemically determined information is used for detection of allelic polymorphisms.

22. (Currently Amended) A method as claimed in ~~any one of the preceding claims~~claim 1 wherein the electrochemically determined information is used for the detection of single nucleotide polymorphisms.

23. (Currently Amended) A method as claimed in ~~any one of claims 1 to 19~~claim 1 wherein the electrochemically determined information is used for the quantification of nucleic acid species.

24. (Currently Amended) A method as claimed in ~~any one of claims 1 to 19~~claim 1 wherein the electrochemically determined information is used for the quantification of gene expression.

25. (Currently Amended) A method as claimed in ~~any one of claims~~claim 16 ~~to 24~~ wherein primer design and/or probe design and/or thermal cycling and detection of electrochemically active marker is carried out automatically or with the assistance of a software-directed microprocessor.

26. (Currently Amended) A method of detecting a specific protein or group of proteins, comprising:

contacting a protein solution with an oligonucleotide probe ~~labelled~~labeled with an electrochemically active marker~~,~~;

providing conditions at which the probe is able to bind to any specific protein or group of proteins that may be present in the solution~~,~~;

selectively degrading ~~unhybridised~~unhybridized nucleic acid probe~~,~~; and

electrochemically determining information relating to the electrochemically active marker in order to provide information about the presence, absence or relative or absolute amounts of the specific target protein or group of target proteins present in said solution.

27. (Original) A method as claimed in claim 26 wherein the oligonucleotide probe sequence is substantially similar to an in vivo protein recognition site and the protein or group of proteins potentially detected would ordinarily be regarded as a nucleic acid binding protein(s).

28. (Original) A method as claimed in claim 26 wherein the oligonucleotide probe comprises an aptamer which has been selected to bind to a specific protein or group of proteins.

29. (Currently Amended) A method as claimed in ~~any one of claims~~claim 24 ~~to 28~~ wherein the ~~unhybridised~~unhybridized nucleic acid is degraded by an enzyme.

30. (Original) A method as claimed in claim 29 wherein the enzyme is an endonuclease.

31. (Currently Amended) A method as claimed in claim 29 ~~or claim 30~~ wherein the enzyme is a ribonuclease.

32. (Currently Amended) A method as claimed in ~~any one of claims~~claim 29 ~~to 31~~ wherein the enzyme is a deoxyribonuclease.

33. (Currently Amended) A method as claimed in ~~any one of claims~~claim 29 ~~to 32~~ wherein the enzyme is S1 deoxyribonuclease.

34. (Currently Amended) A method as claimed in ~~any one of claims 26 to 33~~claim 26 wherein the electrochemically determined information is used for the detection of protein polymorphisms.

35. (Currently Amended) A method as claimed in ~~any one of claims 26 to 34~~claim 26 wherein the electrochemically determined information is used for the quantification of protein expression.

36. (Currently Amended) A method as claimed in ~~any one of the preceding claims~~claim 26 wherein the electrochemical ~~method~~step is voltammetry.

37. (Currently Amended) A method as claimed in ~~any one of claims 1 to 35~~claim 26 wherein the electrochemical ~~technique~~step is an amperometric technique.

38. (Currently Amended) A method as claimed in claim ~~35 claims~~26 wherein the ~~method used~~electrochemical step is differential pulse voltammetry.

39. (Currently Amended) A method as claimed in ~~any of the preceding claims~~claim 26 wherein the electrochemical technique utilizes one or more electrodes that have been functionally surrounded by a selectively permeable membrane.

40. (Original) A method as claimed in claim 39 wherein the membrane is selectively permeable on the basis of molecular size.

41. (Currently Amended) A method as claimed in claim 39 ~~or claim 40~~ wherein the membrane is selectively permeable on the basis of charge.

42. (Currently Amended) A method as claimed in ~~any one of~~ claim 39 ~~to 41~~ wherein the membrane is selectively permeable on the basis of hydrophobicity or hydrophilicity.

43. (Currently Amended) ~~Use of a~~A method as claimed in ~~any one of the preceding claims in~~claim 1 wherein the electrochemically determined information is used for the detection of a genetic disease or a genetic disease carrier status or a genetic predisposition to disease.

44. (Currently Amended) ~~Use of a~~A method as claimed in ~~any one of claims 1 to 43~~claim 1 wherein the electrochemically determined information is used to detect or identify a pathogen in a sample.

45. (Currently Amended) ~~Use of a~~A method as claimed in ~~any one of claims 1 to 43~~claim 1 wherein the electrochemically determined information is used to predict a response of an organism to a therapeutic or toxic agent.

46. (Original) A nucleic acid probe molecule comprising an oligonucleotide of specific sequence covalently linked to one or more electrochemically active marker moieties.

47. (Original) A probe as claimed in claim 46 wherein one or more electrochemically active marker moieties are linked to the oligonucleotide via a linker comprising an aliphatic chain having at least 4 carbon atoms.

48. (Currently Amended) A probe as claimed in claim ~~46 or claim 47,~~46, which comprises at least one metallocene moiety.

49. (Currently Amended) A probe as claimed in ~~any one of claims 46 to 48,~~claim 46, which comprises at least one ferrocene moiety.

50. (Currently Amended) A probe as claimed in ~~anyone of claims~~claim 46 ~~to 49~~ wherein the oligonucleotide component is ~~optimised~~optimized in terms of length or sequence to ~~hybridise~~hybridize to a target nucleic acid sequence.

51. (Currently Amended) A probe as claimed in ~~any one of claims~~claim 46 ~~to 50~~ wherein the oligonucleotide component is ~~optimised~~optimized in order to ~~hybridise~~hybridize to a target DNA sequence at a position intermediate between a matched pair of oligonucleotide PCR primers, so that upon primer extension the oligonucleotide component of the probe may be digested by a 5' nuclease activity of the thermostable DNA polymerase.

52. (Currently Amended) A probe as claimed in ~~any one of claims~~claim 46 ~~to 50~~ wherein the oligonucleotide component is ~~optimised~~optimized in order to partially ~~hybridise~~hybridize to a target nucleic acid sequence at a position which overlaps with a second ~~hybridised~~hybridized oligonucleotide, the overlap region being situated towards

the 5' end of the probe, said 5' end being prevented from complete ~~hybridisation~~hybridization to the target nucleic acid by the presence of the second oligonucleotide.

53. (Currently Amended) A probe as claimed in ~~any of claims~~claim 46 ~~to 52~~ wherein said probe is a recognition cassette ~~labelled~~labeled with an electrochemically active marker and ~~optimised~~optimized to ~~hybridise~~hybridize to a target nucleic acid sequence so as to form a region of nucleic acid triplex which can be specifically ~~recognised~~recognized by an enzyme, said recognition resulting in cleavage of said recognition cassette.

54. (Currently Amended) A probe as claimed in ~~any one of claims~~claim 46 ~~to 49~~ wherein the nucleic acid component is ~~optimised~~optimized in terms of length or sequence to ~~hybridise~~hybridize to a target protein.

55. (Original) A probe as claimed in claim 54 wherein the probe comprises an aptamer.

56. (Currently Amended) A probe claimed in claim 54 ~~or claim 55~~ wherein the probe substantially comprises the nucleic acid sequence of a naturally occurring protein recognition site.

57. (Currently Amended) A probe as claimed in ~~any one of claims~~claim 46 ~~to 56~~ wherein an electrochemically active marker is attached to the 3' end of the oligonucleotide probe.

58. (Currently Amended) A probe as claimed in ~~any one of claims~~claim 46 ~~to 57~~ wherein an electrochemically active marker is attached to the 5' end of the oligonucleotide probe.

59. (Currently Amended) A probe as claimed in any one of ~~claims~~claim 46 ~~to 58~~ wherein multiple electrochemically active markers are attached along the length of the oligonucleotide probe.

60. (Currently Amended) A probe as claimed in ~~any one of claims~~claim 46 ~~to 59~~ wherein an electrochemically active marker is attached to substantially all of nucleotide residues of the oligonucleotide probe.

61. (Canceled)

62. (Canceled)

63. (Currently Amended) A probe as claimed in ~~any one of claims~~claim 46 ~~to 62~~ wherein the oligonucleotide component is phosphorylated at both the 3' and 5' ends.

64. (Currently Amended) A kit comprising an oligonucleotide ~~labelled~~labeled with an electrochemically active marker and any one or more other component selected from oligonucleotide primers or enzymes ~~optimised~~optimized for use with the ~~labelled~~labeled oligonucleotide in accordance with ~~any of the preceding~~ method ~~or use claims~~of claim 1.

65. (Currently Amended) A kit as claimed in claim 64, comprising an oligonucleotide probe ~~labelled~~labeled with an electrochemically active marker and S1 nuclease.

66. (Original) A kit as claimed in claim 64, comprising an oligonucleotide probe and a pair of PCR primers.

67. (Currently Amended) A kit as claimed in claim ~~64 or claim 66,~~64, comprising a nucleic acid polymerase that exhibits a 5' nuclease activity.

68. (Canceled)

69. (Currently Amended) ~~Apparatus~~An apparatus comprising:

one or more sample receiving regions for receiving one or more ~~sample~~samples;

control means for controlling the temperature of said sample receiving regions; and

measuring means for measuring the electrochemical properties of said samples.

70. (Currently Amended) ~~Apparatus~~An apparatus as claimed in claim 69, wherein the apparatus comprises a thermal cycler.

71. (Currently Amended) ~~Apparatus~~An apparatus as claimed in claim ~~69 or 70~~,69, wherein the measuring means comprises an apparatus for voltammetry.

72. (Canceled)

73. (Canceled)

74. (Canceled)

75. (Currently Amended) A compound ~~of~~having a formula ~~XI~~:

Mc-NR'-C(=O)-X-(Ar)n-(L)m-R~~————————XI~~

Wherein

- Mc is a metallocenyl group in which each ring may independently be substituted or unsubstituted,

- the metallocenyl group comprises a metal ion M selected from the group consisting of iron, chromium, cobalt, osmium, ruthenium, nickel or titanium,

- R' is H or lower alkyl,

- X is either NR' or O,

- Ar is a substituted or unsubstituted aryl group,

- n is 0 or 1,

- L is a linker group,

- m is 0 or 1, and

- R represents a moiety to be ~~labelled~~labeled or R is a moiety comprising a leaving group.

76. (Currently Amended) A compound as claimed in claim 75 in which the Mc group is substituted by one or more groups selected from the group comprising lower alkyl (for example C1 to C4 alkyl), lower alkyl substituted with a hydroxy, halo, cyano, oxo, amino, ester or amido group, lower alkenyl, lower alkenyl substituted with a hydroxy,

halo, cyano, oxo, amino, ester or amido group, aryl or aryl substituted with a hydroxy, halo, cyano, oxo, amino, ester or amido group.

77. (Original) A compound as claimed in claim 75 in which the Mc group is unsubstituted.

78. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 77~~ in which M is an iron ion.

79. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 78~~ in which R' is H.

80. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 79~~ in which X is NH.

81. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 80~~ in which n=1.

82. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 80~~ in which n=0.

83. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 82~~ in which m=1.

84. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 82~~ in which m=0.

85. (Currently Amended) A compound as claimed ~~in any one of claims~~claim 75 ~~to 84~~ in which R is a moiety to be ~~labelled~~labeled and R comprises amino acid, nucleotide, nucleoside, sugar, peptide, protein, oligonucleotide, polynucleotide, carbohydrate or derivative of any thereof.

86. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 84~~ in which R is a group comprising a leaving group.

87. (Original) A compound as claimed in claim 86 wherein R is a group comprising N-hydroxysuccinimide.

88. (Currently Amended) A compound as claimed in ~~any one of claims~~claim 75 ~~to 85~~ wherein R comprises an oligonucleotide having a sequence that enables it to hybridize with a target.

89. (Currently Amended) A compound as claimed in ~~any of claims 75 to 88,~~claim 75, wherein the compound is electrochemically active or becomes electrochemically active following partial cleavage.

90. (Currently Amended) A compound as claimed in ~~any of claims 75 to 89,~~claim 75, wherein the metallocene group is substituted by any other electrochemically active marker group.

91. (Currently Amended) A method as claimed in ~~any one of claims~~claim 1 ~~to 42~~ in which two or more oligonucleotide probes are used, each probe being ~~labelled~~labeled with a different electrochemically active marker.

92. (Original) A method as claimed in claim 91 in which the two or more electrochemically active markers have peaks in their voltammogram traces that are resolvable from each other.

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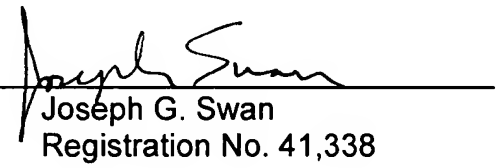
Respectfully submitted,

MITCHELL, SILBERBERG & KNUPP LLP

Dated: September 7, 2004

By 
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